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Regional atrophy is associated with impairment in distinct cognitive domains in Alzheimer's disease

Lieke L. Smits[a,*], Betty M. Tijms[a], Marije R. Benedictus[a], Esther L. G. E. Koedam[a], Teddy Koene[b], Ilona E. W. Reuling[b], Frederik Barkhof[c], Philip Scheltens[a], Yolande A. L. Pijnenburg[a], Mike P. Wattjes[c], Wiesje M. van der Flier[a,d]

[a]*Alzheimer Center and Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands*
[b]*Alzheimer Center and Department of Medical Psychology, VU University Medical Center, Amsterdam, The Netherlands*
[c]*Alzheimer Center and Department of Radiology, VU University Medical Center, Amsterdam, The Netherlands*
[d]*Alzheimer Center and Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands*

Abstract

Background: In Alzheimer's disease (AD), some patients present with cognitive impairment other than episodic memory disturbances. We evaluated whether occurrence of posterior atrophy (PA) and medial temporal lobe atrophy (MTA) could account for differences in cognitive domains affected.

Methods: In 329 patients with AD, we assessed five cognitive domains: memory, language, visuospatial functioning, executive functioning, and attention. Magnetic resonance imaging (MRI) was rated visually for the presence of MTA and PA. Two-way analyses of variance were performed with MTA and PA as independent variables, and cognitive domains as dependent variables. Gender, age, and education were covariates. As PA is often encountered in younger patients, analyses were repeated after stratification for age of onset (early onset, $\leq$ 65 years).

Results: The mean age of the participants was 67 years, 175 (53%) were female, and the mean Mini-Mental State Examination (score $\pm$ standard deviation) was 20 $\pm$ 5 points. Based on dichotomized magnetic resonance imaging ratings, 84 patients (26%) had MTA and PA, 98 (30%) had MTA, 57 (17%) had PA, and 90 (27%) had neither. MTA was associated with worse performance on memory, language, and attention (all, $P < .05$), and PA was associated with worse performance on visuospatial and executive functioning (both, $P < .05$). Stratification for age showed in patients with late-onset AD (n = 173) associations between MTA and impairment on memory, language, visuospatial functioning, and attention (all, $P < .05$); in early-onset AD (n = 156), patients with PA tended to perform worse on visuospatial functioning.

Conclusions: Regional atrophy is related to impairment in specific cognitive domains in AD. The prevalence of PA in a large set of patients with AD and its association with cognitive functioning provides support for the usefulness of this visual rating scale in the diagnostic evaluation of AD.
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Keywords: Alzheimer's disease; Magnetic resonance imaging; Visual rating scales; Neuropsychology; Cognition

1. Introduction

Alzheimer's disease (AD) is increasingly considered a heterogeneous disease that may present initially with cognitive decline other than pronounced memory impairment [1–3]. Besides memory impairment, AD may also feature nonamnestic presentations with prominent dysfunction in language, visuospatial functions, or executive functions. These atypical presentations are also recognized in the new clinical criteria for AD [4].

On magnetic resonance imaging (MRI), atrophy of the medial temporal lobe, especially the hippocampus, is considered a diagnostic hallmark of AD, and relations with episodic memory impairment have been shown frequently [5–7]. Medial temporal lobe atrophy (MTA) can be scored using

*Corresponding author. Tel.: +31 20 4440685; Fax: +31 20 4440715.
E-mail address: l.smits@vumc.nl

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a visual rating scale [8], which shows good association with episodic memory and is widely used in clinical practice [7–9].

Nevertheless, not every patient with AD presents with MTA. Imaging studies have revealed prominent (fronto-)parietal atrophy in AD, especially in patients with an earlier age of onset [10–12]. Patients with posterior cortical atrophy (PCA) form a distinct subgroup, presenting with prominent visual problems, but posterior atrophy (PA) seems to be far more frequent in AD [13]. Recently, we developed a new visual rating scale for PA that allows for easy use in clinical practice [14,15]. It has been shown that PA discriminates early-onset patients with AD from younger control subjects independent of MTA [15]. It is attractive to assume that this scale is associated with cognitive impairment in AD, especially nonamnestic signs and symptoms, but this has not yet been proved.

In the current study, we therefore assessed associations between visual ratings of MTA and PA and cognitive impairment in a large set of patients with AD. In addition, we stratified the analyses at age of onset, because PA is observed relatively often in early-onset AD.

2. Methods

2.1. Subjects

Consecutive patients (n = 344) with probable AD were included from the outpatient memory clinic of the Alzheimer Center of the VU University Medical Center (VUmc) between August 2008 and January 2012. For the diagnostic procedure, all patients underwent a standardized 1-day assessment, including medical history and family history for dementia, informant-based history, physical and neurological examinations, neuropsychological assessment, laboratory tests, electroencephalogram, and MRI of the brain. Diagnoses were made in a multidisciplinary consensus meeting. All patients fulfilled the core clinical criteria for probable AD of the National Institute on Aging–Alzheimer's Association [4]. Inclusion criteria for this study were a diagnosis of probable AD and available Mini-Mental State Examination (MMSE) score, Cambridge Cognitive Examination (CAMCOG) score, and neuropsychological assessment. Exclusion criteria were frank vascular abnormalities (n = 10) and missing MRI sequences (n = 5). This resulted in a total study sample of 329 patients. Level of education was classified according to the system of Verhage, ranging from 1 to 7 points (low to highly educated) [16]. The study was conducted in accordance with regional research regulations and conformed to the Declaration of Helsinki. The local medical ethics committee approved the study, and all patients gave written informed consent for their clinical data to be used for research purposes.

2.2. Neuropsychological assessment

Cognitive functions were assessed with a standardized test battery, covering several cognitive domains. We used the MMSE and the CAMCOG for global cognitive decline [17,18]. For memory, we used the Visual Association Test (VAT), and total immediate recall and delayed recall of the Dutch version of the Rey Auditory Verbal Learning Task (RAVLT) [19–21]. To examine language, we used VAT naming, category fluency (animals), and the Dutch version of the Controlled Oral Word Association Test (letter fluency) [19,22,23]. We used three subtests of the Visual Object and Space Perception Battery to assess visuospatial functioning—namely, incomplete letters, dot counting, and number location [24]. For the attention domain we used Trail Making Test (TMT) A and the forward condition of digit span (extended version) [25,26]. We used TMT B and the backward condition of digit span (extended version) to examine executive functioning [25,26].

2.3. MRI and image analysis

MRI was performed on a 3.0-T magnetic resonance system (Signa HDxt; General Electric, Milwaukee, WI). All subjects were examined according to a standard dementia MRI protocol, including sagittal, T1-weighted three-dimensional (3D) fast spoiled gradient echo sequences (field of view [FOV], 25 cm; matrix, 256 × 256; 1-mm slices; echo time, 3 ms; repetition time, 7.8 ms; inversion time, 450 ms; one signal acquired), 3D fluid-attenuated inversion recovery (FLAIR) sequences (FOV, 25 cm; matrix, 224 × 224; 1.2-mm slices; echo time, 140 ms; repetition time, 8000 ms; inversion time, 2349 ms; echo train length, 230; one signal acquired), and axial fast spin-echo T2/PD (Proton Density) sequences (FOV, 25 cm; matrix, 384 × 384; 3-mm slices; echo time, 23/114 ms; repetition time, 9100 ms; echo train length, 24; two signals acquired). Multiplanar reconstructions of 3D T1-weighted sequences were performed in sagittal (5 mm) and oblique–coronal orientations (3-mm slices perpendicular to the long axis of the hippocampus). Multiplanar reconstructions of 3D FLAIR images were performed in transverse orientation using a 3-mm section thickness.

The image analysis included a visual rating of MTA and PA [8,14]. T1-weighted images were viewed in the coronal plane, and MTA scores for the left and right hemispheres were given. The scale rates atrophy on a 5-point scale (0 point, absent; 1 point, minimal; 2 points, mild; 3 points, moderate; and 4 points, severe) based on the height of the hippocampal formation and the width of the choroid fissure and the temporal horn [8]. PA scoring was based on the axial multiplanar reconstruction of the FLAIR sequences, and the coronal and sagittal reconstructions of the 3D T1-weighted sequence. The PA scale rates atrophy on a 4-point scale (0 point, absent; 1 point, mild sulcal widening and mild atrophy; 2 points, substantial widening and substantial atrophy; and 3 points, end-stage atrophy) based on the posterior cingulate- and parieto-occipital sulcus and sulci of the parietal lobes and precuneus [14]. MTA and PA scores were dichotomized into relevant atrophy present

Table 1
Demographics and pooled neuropsychological test performance of patients with or without MTA or PA

Characteristic	All patients	MTA		PA	
		No atrophy	Atrophy	No atrophy	Atrophy
n	329	147	182	188	141
Women, n (%)	175 (53)	84 (57)	92 (50)	103 (54)	73 (52)
Age, y; mean ± SD	67 ± 8	65 ± 7	69 ± 8*	67 ± 7	66 ± 9
Level of education, mean ± SD†	5 ± 1	5 ± 1	5 ± 1	5 ± 1	5 ± 1*
MMSE score, pt; mean ± SD	20 ± 5	20 ± 5	19 ± 6	20 ± 5	20 ± 5
CAMCOG score, pt; mean ± SD	66 ± 17	68 ± 15	64 ± 18*	67 ± 17	65 ± 17
Memory score, pt; mean ± SD					
VAT	5 ± 4	6 ± 4	5 ± 4	5 ± 4	5 ± 4
RAVLT, total immediate recall‡	20 ± 7	21 ± 9	19 ± 8*	20 ± 8	20 ± 9
RAVLT, delayed recall‡	2 ± 2	2 ± 2	1 ± 2	1 ± 2	2 ± 2
Language score, pt; mean ± SD					
VAT naming	11 ± 1	11 ± 2	11 ± 2	11 ± 2	11 ± 2
Category fluency	12 ± 5	12 ± 5	11 ± 6	12 ± 6	11 ± 6
Letter fluency	24 ± 11	24 ± 11	24 ± 12	24 ± 12	24 ± 12
Visuospatial functioning score, pt; mean ± SD					
Incomplete letters	14 ± 5	14 ± 6	14 ± 7*	14 ± 6	13 ± 6
Dot counting	9 ± 1	9 ± 2	9 ± 1	9 ± 1	9 ± 2
Number location	8 ± 2	8 ± 2	8 ± 2	8 ± 2	7 ± 2
Executive functioning score, pt; mean ± SD					
TMT B§	270 ± 208	274 ± 135	268 ± 128	264 ± 138	280 ± 122
Digit span backward	6 ± 3	6 ± 3	6 ± 3	6 ± 3	6 ± 2*
Attention score, pt; mean ± SD					
TMT A§	106 ± 62	107 ± 77	106 ± 73	101 ± 74	113 ± 76
Digit span forward	10 ± 3	11 ± 3	10 ± 3*	10 ± 3	11 ± 3

Abbreviations: MTA, medial temporal lobe atrophy; PA, parietal atrophy; SD, standard deviation; MMSE, Mini-Mental State Examination; CAMCOG, Cambridge Cognitive Examination; VAT, Visual Association Test; RAVLT, Rey Auditory Verbal Learning Task; TMT, Trail Making Test.

NOTE. Two-way analyses of variance were performed with MTA and PA as a between-subject factor. Gender, age, and education were entered as covariates.

*$P < .05$.

†According to the Verhage system.

‡Dutch version of the RAVLT.

§Higher scores imply worse performance.

or absent based on a mean score for left and right of 1.5 points or more.

2.4. Statistical analysis

Because complete case analysis (exclusion of all patients with one or more missing neuropsychological tests) leads to loss of statistical power and biased results, we imputed the data [27,28]. There was variance in the number of completed neuropsychological tests. On average, every test was completed by 260 patients, ranging from 306 (digit span forward) to 148 (TMT B). Tests were not finished because of cognitive impairment or lack of time. We used the software package Multivariate Imputation by Chained Equations (version 2.14.1 [29]) in the statistical program R (version 3.0.0) to perform multiple imputations of the data. Briefly, this method uses fully conditional specification, which constructs multivariate imputation models with a set of conditional densities for each variable. Age, gender, and education level were included as predictor variables in addition to the neuropsychological test scores for imputation of the missing values.

We report pooled statistics over five imputed data sets. PASW Statistics 18.0 for Mac was used. TMT A and B scores were log-transformed because they were not distributed normally. All neuropsychological data were standardized into z scores to allow comparison of different neuropsychological tests within patients. TMT A and B scores were inverted by computing $-1 \times$ z score, because higher scores imply a worse performance. For each of the five cognitive domains, the mean z scores for the corresponding tests were calculated. Independent sample t tests and χ^2 tests were conducted when appropriate. To assess the relationships between MTA and PA and cognitive functions, we used two-way analyses of variance (ANOVA), with MTA and PA as independent variables, and composite domain scores as dependent variables. Gender, age, and education were entered as covariates. When there were no significant interactions, pooled P values were derived from the model without interaction terms. We repeated the two-way ANOVA after stratification based on age at diagnosis: early-onset AD (65 years or younger) and late-onset AD (older than 65 years). For all analyses, the significance level was set at $P < .05$.

3. Results

In the total sample, age (mean ± standard deviation) was 67 ± 8 years, and 175 patients (53%) patients were female (see Table 1 for demographics). Mean MMSE score was

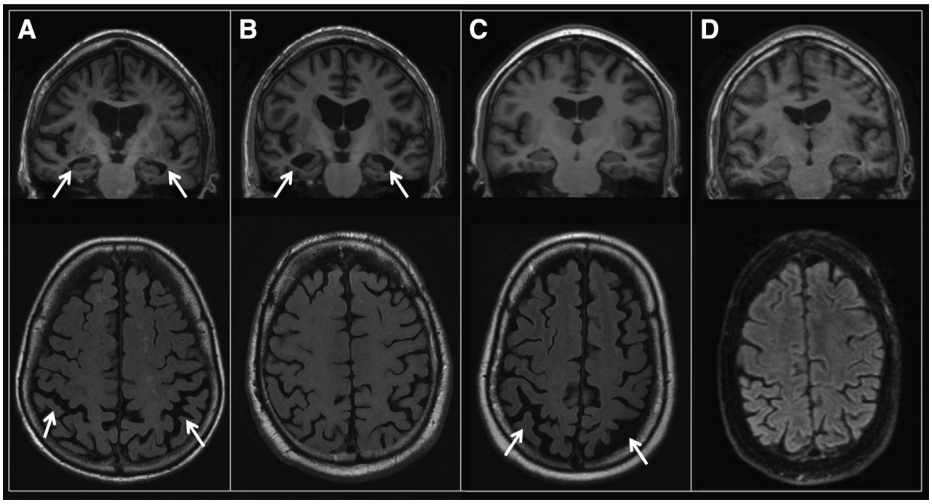

Fig. 1. Illustrative magnetic resonance images (coronal T1 and axial fluid-attenuated inversion recovery) of four patients with Alzheimer's disease and comparably mild dementia (Mini-Mental State Examination score for all patients was 23 points). (A) Patient with both medial temporal lobe atrophy (MTA) and posterior atrophy (PA). This 77-year-old woman visited our memory clinic for a second opinion. Neuropsychological assessment revealed impairment of memory and visuospatial functioning, and some executive impairment, including impaired flexibility. On magnetic resonance imaging (MRI), MTA grade 2 (both hemispheres) and PA grade 2 (both hemispheres) were seen. Also, a Fazekas score of 2 points was noted. (B) Patient with MTA in absence of PA. This 78-year-old man visited our memory clinic and reported memory complaints and difficulties with word finding for the past 3 years. Neuropsychological assessment showed clear impairments in memory and word finding, and some limitations in the other cognitive domains. MRI showed MTA grade 4 (both hemispheres), no PA, and some punctate white matter abnormalities. (C) Patient with PA in the absence of MTA. This 57-year-old woman visited our memory clinic for a third opinion. Earlier investigations did not yield a diagnostic conclusion. She was not able to work anymore because of her memory complaints. Her husband reported additional troubles with word finding and attention; nevertheless, she could function on her own. Neuropsychological assessment showed impairment in memory and visuospatial functioning. On MRI, major PA and atrophy of the precuneus and posterior cingulate were seen. The medial temporal lobes also showed mild atrophy (both hemispheres, grade 1). (D) Patient with no atrophy. This 62-year-old man visited our memory clinic for further research regarding his cognitive complaints of forgetfulness and difficulty reading digital clocks. Neuropsychological assessment found impairments in memory, language, and executive functioning. MRI showed no abnormalities, with the exception of minimal PA. Additionally, a Pittsburgh compound B positron emission tomographic scan showed amyloid depositions and in the cerebrospinal fluid, decreased amyloid β and slightly increased tau was observed.

20 ± 5 points and mean CAMCOG score was 66 ± 17 points. Based on dichotomized MRI ratings, 84 subjects (26%) had both MTA and PA, 98 (30%) had MTA only, 57 (17%) had PA only, and 90 (27%) had no atrophy. Fig. 1 shows examples of patients with these specific atrophy patterns, all with comparably mild dementia (MMSE score, 23 points).

In total, 85 subjects completed all neuropsychological tests, and 244 patients missed at least one test. There was no difference in gender distribution between these two groups (complete, 49% female; missing, 55% female; $P = .49$), nor was there a difference in age (complete, 68 ± 7 years; missing, 67 ± 8 years; $P = .35$). The complete group had a slightly higher level of education than the incomplete group (complete, level of education 5.2 ± 1.2; missing, level of education 4.7 ± 1.3; $P = .001$). The complete group had less severe cognitive impairment, as evidenced by higher MMSE scores, than the missing group (complete, 23 ± 3 points; missing, 19 ± 5 points). Regarding MRI, both groups had comparable presence of MTA (complete, 55%; missing, 55%; $P = 1.0$), and people with missing values were more likely to have PA (complete, 32%; missing, 46%; $P = .04$). Table 1 also shows the raw neuropsychological test results according to presence of MTA and PA. Patients with MTA performed worse on total immediate recall of the Dutch RAVLT ($P < .05$), incomplete letters ($P < .05$), and digit span forward ($P < .01$) than patients without MTA. Patients with PA performed worse on digit span backward than patients without PA ($P < .01$). Regarding other cognitive tests, we found no differences between patients with or without MTA, or patients with or without PA.

Subsequently, we used two-way ANOVA to assess the combined effects of MTA and PA on functioning in cognitive domains, with gender, age, and education as covariates. There were no significant interactions between MTA and PA. Therefore, pooled P values were derived from models without interaction terms. We found that patients with MTA performed worse on memory ($P < .01$), language ($P < .05$), and attention ($P < .05$) compared with patients without MTA. There was no relation between MTA and visuospatial functioning ($P = .12$) or executive functioning ($P = .24$). Patients with PA performed worse on visuospatial functioning ($P < .05$) and executive functioning ($P < .05$) compared with patients without PA. There was no relation between PA and memory ($P = .67$) or language ($P = .19$). Fig. 2 illustrates that, according to presence of MTA and/or PA, groups show different cognitive profiles; patients with no atrophy showed relatively less impaired performance in comparison with the other groups. Patients with MTA were most impaired on memory. Patients with PA showed relatively good memory and performed worse on visuospatial functioning and executive functioning.

Patients with MTA and PA in general performed worse on neuropsychological testing compared with other groups, with most prominent impaired performance on language, visuospatial functioning, and attention.

Next, we stratified the analysis for age, creating two groups: early-onset AD (n = 156) and late-onset AD (n = 173). Table 2 shows the demographics of both groups. Patients with early-onset AD performed worse on the MMSE and the CAMCOG than patients with late-onset AD. Patients with late-onset AD had more severe MTA than early-onset patients. The degree of PA in patients with early-onset AD, however, was just as severe as in those with late-onset AD. In early-onset AD, there was no relation between MTA and any cognitive domain. The performance of patients with early-onset AD with PA on visuospatial functioning tended to be worse than younger patients without PA ($P = .055$). We did not find any other relation with PA in patients with early-onset AD, nor were there any interactions between MTA and PA. In late onset AD, patients with MTA performed worse on memory ($P < .01$), language ($P < .05$), visuospatial functioning ($P < .05$), and attention ($P < .01$) than older patients without MTA. There was no relation between MTA and executive functioning, nor was there a correlation between PA and cognitive functioning. There were no interactions between MTA and PA in patients with late-onset AD.

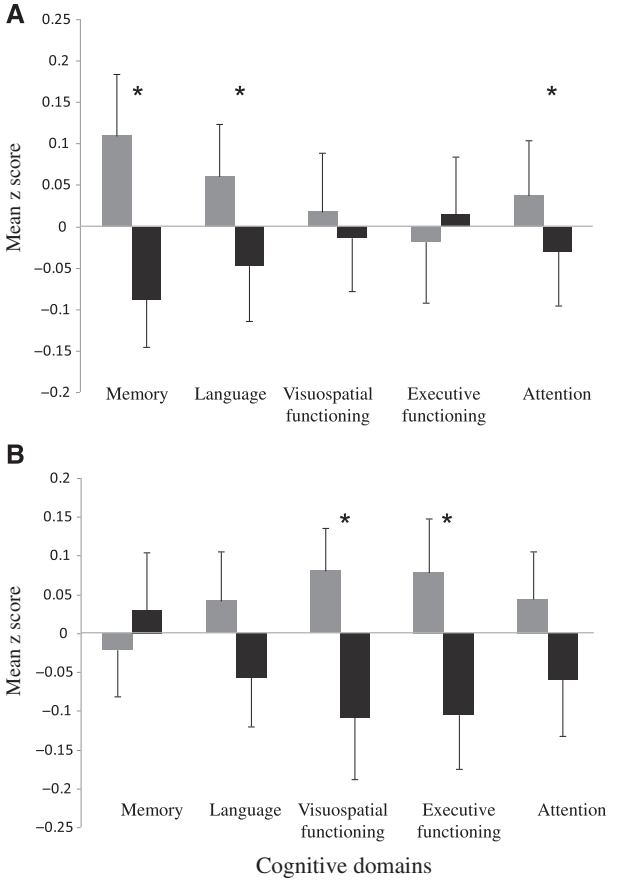

Fig. 2. Mean neuropsychological z scores according to medial temporal lobe atrophy (MTA) and parietal atrophy (PA). The *x*-axis shows the five cognitive domains: memory, language, visuospatial functioning, executive functioning, and attention. (A) Mean z scores for patients with no MTA (gray bars, n = 147) compared with patients with MTA (black bars, n = 182; upper panel). (B) Mean z scores for patients with no PA (gray bars, n = 188) and with PA (black bars, n = 141). We performed two-way analysis of variance to assess the combined effects of MTA and PA on functioning in cognitive domains, using gender, age, and education as covariates. *Significant main effect ($P < .05$).

4. Discussion

Using simple visual rating scales, we showed that MTA was associated with impaired memory, language, and attention, whereas PA was associated with impaired visuospatial functioning and executive functioning. These findings provide evidence that, despite comparable disease severity, clinical heterogeneity can be related to variability in regional atrophy in AD.

The visual rating scale for MTA has been used for more than two decades now in both research and clinical settings [9,30]. It is increasingly acknowledged that evaluation of MRI in the context of AD should not be restricted to the medial temporal lobe. To facilitate use in clinical practice, we recently developed a visual rating scale for PA, but its clinical use has not yet been established. We used both scales in a large cohort of patients with AD, and found that MTA and PA are both observed frequently, together as well as in isolation. In our cohort, 17% of patients had PA in absence of MTA, which is less than in two former studies in which the numbers were 28% and 30%, respectively [14,15]. This difference can probably be explained by the fact that, on average, patients in the current study were older than in one former study [15], while PA in isolation is more often observed in younger patients [10–12,31].

The association we found between PA and executive functioning at first seems rather counterintuitive, but could be explained in part by worse performance on the TMT B, which—in addition to measuring executive functioning—also relies heavily on intact visuospatial abilities. Furthermore, atrophy of frontoparietal regions influencing executive functioning has been demonstrated before [3]. Until now, only a few studies have been conducted using the PA scale, showing that the scale seems to discriminate AD from dementia with Lewy bodies and frontotemporal lobar degeneration [14]. Furthermore, PA ratings could distinguish between younger control subjects and early-onset AD, but not between older control subjects and late-onset AD [15]. It has been suggested that in patients with mild cognitive impairment, the MTA and PA scale may offer independent and complementary predictive information regarding to conversion to AD [32]. In the current study, we found that PA occurs in both early-onset and late-onset AD. Associations in the stratified analysis were no longer significant, probably as a result of a lack of power. Our results are in line with these former findings, showing that ratings on both scales

Table 2
Demographics of patients with early- and late-onset Alzheimer's disease

Characteristic	Early onset	Late onset
n	156	173
Women, n (%)	90 (58)	85 (49)
Age, y; mean ± SD	60 ± 4	73 ± 5*
Level of education; mean ± SD†	5 ± 1	5 ± 1
Mean MTA ± SD	1.2 ± 0.8	1.6 ± 0.8*
Mean PA ± SD	1.3 ± 0.8	1.3 ± 0.7
MMSE score, pt; mean ± SD	19 ± 5	21 ± 5*
CAMCOG score, pt; mean ± SD	63 ± 17	69 ± 16*

Abbreviations: SD, standard deviation; MTA, medial temporal lobe atrophy; PA, parietal atrophy; MMSE, Mini-Mental State Examination; CAMCOG, Cambridge Cognitive Examination.

NOTE. Independent sample *t* tests and χ^2 tests were performed with onset as a between-subject factor.

*$P < .05$.

†According to the Verhage system.

are related to cognitive impairment, albeit in different domains, which emphasizes their complementary value.

The visual ratings of MTA and PA are easy to assess, and the results are in accordance with more sophisticated methods, such as volumetric MRI or voxel-based morphometry. A study in prodromal AD showed that patients had mainly MTA, which was associated with severe memory impairment [5]. Another study in which patients with AD were divided into typical and atypical subgroups, based on their neuropsychological performance, found that nonmemory problems in AD were associated with thinning of the right superior parietal lobe, whereas memory impairment was related to thinning of the left entorhinal cortex [33]. In addition, in a former study conducted by our own group, in a completely independent sample, atrophy of the precuneus was related specifically to impaired visuospatial functioning [11]. A volumetric study found, in AD, associations between MTA and memory impairment, and PA and praxis in AD [6].

A possible limitation of this study may be that we did not have postmortem data available, so the possibility of misdiagnosis cannot be ruled out. Nevertheless, we had an extensive standardized workup, and all patients fulfilled core clinical criteria of probable AD. Furthermore, in our neuropsychological assessment no specific tests for praxis and gnosis were included, although these cognitive domains also seems specifically related to PA. One of the strengths of this study is that we imputed the missing neuropsychological data. In this way, we avoided selection bias that would be created by using only complete neuropsychological assessments. Further strengths are the large cohort of patients with AD with available magnetic resonance images, and the standardized neuropsychological test battery, including tests assessing visuospatial functioning.

Benson and colleagues [13] were one of the first to describe PCA as a very exceptional syndrome. Lately, it has been suggested that PCA can be considered an independent nosology, with AD as the most common underlying cause [34]. Our results show that an observation of PA on MRI is not restricted to the rare and highly specific cases of patients with PCA. Rather, in the spectrum of AD, PA is a frequently observed MRI characteristic in both early and late onset. Furthermore, our results seemingly suggest that PA predisposes for specific nonmemory symptoms. These symptoms are relatively often encountered in patients with early-onset AD, providing additional relevance for using the visual rating scale in this group. Our results suggest that the visual rating scale for PA is a promising diagnostic tool in addition to the MTA scale, especially when taking into account the new clinical criteria for AD, which include nonamnestic presentations as well [4].

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RESEARCH IN CONTEXT

1. Systematic review: The heterogeneity of AD, that goes beyond clinical presentation, asks for new diagnostic tools. PubMed was used for literature search. Studies solely including patients with AD were prioritized. No previous cross-sectional study assessing visual rating scales for medial temporal lobe atrophy (MTA) and parietal atrophy (PA) in association with cognitive impairment in patients with AD was identified.
2. Interpretation: The recently developed MRI scale to visual rate PA is easy to use in clinical practice. This is a promising tool; we found that many patients with AD show PA, while their medial temporal lobe is still relatively unharmed. We show that MTA and PA are related to impairment in specific cognitive functions, providing validation of the scale.
3. Future directions: Future research should attempt to 1) further correlate the PA rating scale with clinical heterogeneity 2) investigate the associations between pattern of atrophy and cognition longitudinally to achieve better understanding of the heterogeneity in the spectrum of AD 3) validate the scale in other forms of dementia e.g. Dementia with Lewy bodies.

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